Remarks

The Office Action mailed 11 April 2001 has been received and reviewed. The application is to be amended as previously set forth. New claims 44 through 58 are to be added. Claim 15 is to be canceled. All amendments, including the cancellation of claims, have been made without prejudice or disclaimer. Claims 1, 2, 4 through 21, 24 through 26, 28 through 32, and 37 through 43 are identified as pending in the Office Action dated 11 April 2001. All claims stand rejected. Reconsideration is respectfully requested.

1. Minor Informalities

Claim 26 has been amended to set forth the claimed subject matter more clearly per the Examiner's suggestion.

2. 35 U.S.C. § 112, Second Paragraph, Rejections

A. Rejection of claims 1, 4-11, 13-18, 21, and 43 under 35 U.S.C. § 112, second paragraph

Claims 1, 4-11, 13-18, 21, and 43 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Applicants have amended claim 1 to clarify the claim. In addition, independent claims 19, 24, and 26 have been amended to reflect the amendment of claim 1. Applicants respectfully submit that the remaining claims, as indirectly or directly depending from claim 1, are definite, and accordingly respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Rejection of claims 2, 38-40, and 42 under 35 U.S.C. § 112, second paragraph

Claims 2, 38-40, and 42 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite with respect to the terminology "deprived". Claim 2 has accordingly been amended to remove the rejected terminology which should overcome the rejection. As claims 38-40 and 42 indirectly or directly depend from claim 2, these claims too should be considered definite. Applicants respectfully request the rejection under 35 U.S.C. § 112, 2nd ¶ be withdrawn.

C. Rejection of claims 10, 15, and 20 under 35 U.S.C. § 112, second paragraph

Claims 10, 15, and 20 were rejected under 35 U.S.C. § 112, second paragraph, as

assertedly being indefinite. Specifically the Examiner objected to the use of the term "derived." Applicants have amended claims 10 and 20 to remove the terminology, and, in view of the amendments, respectfully request that the rejection be withdrawn. Claim 15 has been cancelled, rendering the rejection as to that claim moot.

D. Rejection of claim 12 under 35 U.S.C. § 112, second paragraph

Claims 12 was rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to recite the claim number on which it depends. Claim 12 has been amended to recite the claim number from which it depends, and, accordingly, applicants respectfully request the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

E. Rejection of claim 29-31 under 35 U.S.C. § 112, second paragraph

Claims 29-31 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants agree that a discrepancies exist in the exact sequence of adenovirus type 5 with respect to sequences submitted to GenBank. However, one of skill in the art is aware of the fact that minor differences occur in GenBank sequences such as sequences relating to large genomic fragments like those identified from adenoviral serotypes.

In order to clarify the matter, applicants can state that several accession numbers exist relating to sequences of the Ad5 genome, all of which are believed to differ somewhat. In the present application however, the nucleotide sequences refer to the commonly used GenBank accession number M73260. Thus, the ranges recited in claims 28 to 32 are equivalent to the numbering in GenBank accession number M73260 (except 32794-35938, which sequence is equivalent to 32794-35935 given in M73260). In view of this explanation, applicants respectfully request the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn. In addition, claim 28 which also refers to the adenovirus 5 sequences has been amended to include the reference to the GenBank accession number.

3. 35 U.S.C. § 112, First Paragraph, Rejections

A. Rejection of claims 2, 25, 37-40, and 42 under 35 U.S.C. § 112, first paragraph

Claims 2, 35, 37-40, and 42 were rejected under 35 U.S.C. § 112, 1st ¶, as allegedly

containing subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants have amended claims 2, 25, and 37 and therefore request that the rejection be withdrawn.

Amended Claims 2 and 25 recite the limitation "significantly reduced tissue tropism for liver cells," while amended claim 37 recites "significantly reducing an adenovirus capsid of a tissue tropism for liver cells." Applicants respectfully disagree that "the total amount of transgene activity from all cell types tested is significantly lower in mice infected with the Ad-16 chimera" as compared with the wildtype/control Ad-5. (Office Action, p. 6, lines 3-5). While Table II clearly shows a significantly lower transgene activity in liver and spleen cells, other cell types display similar transgene activity for both the Ad-16 chimera and wildtype/control Ad-5. Claims 2, 25, and 37 have been amended to reflect such results. Accordingly, applicants request that the rejection of claims 2, 25, 38-40, and 42 be withdrawn.

B. Rejection of claim 15 under 35 U.S.C. § 112, first paragraph

As claim 15 has been canceled, the rejection is rendered moot.

C. Rejection of claim 29 through 31 under 35 U.S.C. § 112, first paragraph

Claims 29 through 31 were rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As previously explained, claims 29 through 31 are equivalent to the numbering in GenBank accession number M73260.

Although believed unnecessary by applicants, if it is deemed necessary by the Office, applicants can provide the exact sequence by declaration, or, if more appropriate, by making deposits of the particular cosmids and plasmids under the terms of the Budapest Treaty.

4. 35 U.S.C. § 102

A. Rejection of claims 1, 4-8, 10-14, 16, 17, 19, 24, 26, and 41 under 35 U.S.C. § 102(b)

Claims 1, 4-8, 10-14, 16, 17, 19, 24, 26, and 41 were rejected under 35 U.S.C. §

102(b) as being anticipated by Stevenson et al. (*Journal of Virology*, 71: 4782-4790, 1997) ("Stevenson").

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1990).

Applicants respectfully submit that the presently claimed invention is not anticipated by Stevenson. Independent claim 1, as amended, claims "[a] gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells." In addition, independent claims 19, 24, and 26 have been amended such that these claims are directed at smooth muscle cells, similar to claim 1. In contrast, Stevenson discloses a chimeric adenovirus that has the ability to transduce some types of endothelial cells at a similar or lower level as the Ad-5. (*Stevenson*, Figure 6). However, Stevenson fails to disclose a gene delivery system with the ability to transduce smooth muscle cells. As Stevenson fails to teach every limitation of independent claims 1, 19, 24, or 26, applicants respectfully submit that the claims are not anticipated by the cited reference. Accordingly, applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn with respect to independent claims 1, 19, 24, and 26, and claims 4-8, 10-14, 16, 17, and 41 which depend directly or indirectly therefrom.

5. 35 U.S.C. § 103

A. Rejection of claim 18 under 35 U.S.C. § 103(a)

Claim 18 was rejected under 35 U.S.C. 103(a) as being unpatentable over Stevenson. Claim 18 indirectly depends from independent claim 1. Applicants respectfully traverse the rejection.

M.P.E.P. § 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

> reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or references when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). (Emphasis added).

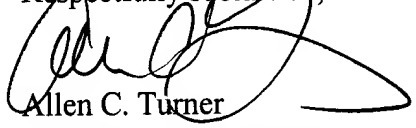
Stevenson teaches a method of using a chimeric adenovirus to transduce human coronary artery endothelial cells at a similar level as "wildtype" adenovirus 5 and transduces human umbilical vein endothelial cells at a lower level than "wildtype" adenovirus 5. (*Stevenson*, Figure 6).

Stevenson fails, however, to render obvious the presently claimed invention because the subject claim limitations are not taught or suggested by Stevenson. Specifically, Stevenson is not believed to teach or suggest transducing "smooth muscle cells." Thus, Stevenson's disclosure fails to establish a *prima facie* case of obviousness because the reference does not teach or suggest all of the claim limitations of the present invention. Therefore, applicants respectfully request that the Examiner withdraw the rejection of unpatentability under 35 U.S.C. § 103(a) of the particularly rejected claim.

Conclusion

In view of the amendments and remarks, applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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VERSION SHOWING CHANGES

1. (Twice amended) A gene delivery vehicle comprising at least a tissue tropism for [cells selected from the group of] smooth muscle cells [, and/or endothelial cells, or smooth muscle cells and epothelial cells].

2. (Twice amended) A gene delivery vehicle [having been deprived of at least a] with a significantly reduced tissue tropism for liver cells.

7. (Twice amended) The gene delivery vehicle of claim 5 wherein at least one of said viruses is [an adenovirus of] a subgroup B adenovirus.

10. (Twice amended) The gene delivery vehicle of claim [7] 5 wherein said virus capsid comprises protein fragments from at least two different viruses and wherein said protein fragments are not [derived] from an adenovirus of subgroup B and are [derived] from an adenovirus of subgroup C.

11. (Twice amended) The gene delivery vehicle of claim 1 further comprising [a] an adenoviral nucleic acid [derived from an adenovirus].

12. (Twice amended) The gene delivery vehicle of claim 11 wherein said [further comprising a] adenoviral nucleic acid comprises sequences originating [derived] from at least two different adenoviruses.

13. (Twice amended) The gene delivery vehicle of claim 11 wherein said adenoviral nucleic acid comprises at least one sequence encoding a fiber protein comprising at least a tissue tropism determining fragment of a subgroup B adenovirus fiber protein.

14. (Twice amended) The gene delivery vehicle of claim 11 wherein said adenoviral nucleic acid [derived from adenovirus] is modified such that the capacity of said [adenovirus] adenoviral nucleic acid to replicate in a target cell has been reduced or disabled.

19. (Twice amended) A cell for producing a gene delivery vector having a tissue tropism for [cells selected from the group of cells consisting of] smooth muscle cells [, endothelial cells, or smooth muscle cells and epothelial cells,] said cell comprising means for the assembly of gene delivery vectors wherein said means includes a means for the production of an adenoviral fiber protein, wherein said adenoviral fiber protein comprises at least a tissue tropism determining fragment of a subgroup B adenoviral fiber protein.

20. (Twice amended) The cell of claim 19, wherein said cell is or [is derived] originates from a PER.C6 cell (ECACC deposit number 96022940).

24. (Twice amended) An adenovirus capsid having a tissue tropism for smooth muscle cells [and/or endothelial cells] wherein said capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is derived from a subgroup B adenovirus.

25. (Twice amended) An adenovirus capsid with a significantly reduced [lacking a] tissue tropism for liver cells wherein said adenovirus capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is derived from a subgroup B adenovirus.

26. (Twice amended) A method of delivering nucleic acid to [cells selected from the group of cells consisting of] smooth muscle cells, [endothelial cells and both smooth muscle and endothelial cells,] said method comprising:
administering to said smooth muscle cells an adenovirus capsid [comprises] comprising proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is derived from a subgroup B adenovirus.

37. (Twice amended) A method of [depriving] significantly reducing an adenovirus capsid of a tissue tropism for liver cells, said method comprising using fiber protein of adenovirus 16 in an adenovirus capsid therefor.

41. (Amended) The gene delivery vehicle of claim 6 wherein at least one of said viruses is [an adenovirus of] a subgroup B adenovirus.

42. (Amended) The gene delivery vehicle of claim 40 wherein at least one of said protein fragments comprises a tissue tropism determining fragment of a fiber protein [derived] from a subgroup B adenovirus.

linked to a promoter. In the latter case E2 and/or E4 complementing cell lines are required to generate recombinant adenoviruses. In fact any gene in the genome of the viral vector can be taken out and supplied in trans. Thus, in the extreme situation, chimaeric viruses do not contain any adenoviral genes in their genome and are by definition minimal adenoviral vectors. In this case all adenoviral functions are supplied in trans using stable cell lines and/or transient expression of these genes. A method for producing minimal adenoviral vectors is described in WO97/00326 and is taken as reference herein. In another case Ad/AAV chimaeric molecules are packaged into the adenovirus capsids of the invention. A method for producing Ad/AAV chimaeric vectors is described in EP 1 042 494 and is taken as reference herein. In principle any nucleic acid may be provided with the adenovirus capsids of the invention.

In one embodiment the invention provides a gene delivery vehicle having been provided with at least a tissue tropism for smooth muscle cells and/or endothelial cells. In another embodiment the invention provides a gene delivery vehicle deprived of a tissue tropism for at least liver cells. Preferably, said gene delivery vehicle is provided with a tissue tropism for at least smooth muscle cells and/or endothelial cells and deprived of a tissue tropism for at least liver cells. In a preferred embodiment of the invention said gene delivery vehicle is provided with a tissue tropism for at least smooth muscle cells and/or endothelial cells and/or deprived of a tissue tropism for at least liver cells using a fiber protein derived from a subgroup B adenovirus, preferably of adenovirus 16. In a preferred aspect of the invention said gene delivery vehicle comprises a virus capsid. Preferably said virus capsid comprises a virus capsid derived in whole or in part from an adenovirus of subgroup B, preferably from adenovirus 16, or it comprises proteins, or parts thereof, from an adenovirus of subgroup B, preferably of adenovirus 16. In a preferred embodiment of the invention